

In view of the above, Applicants respectfully request reconsideration of the Restriction Requirement. Applicants will address the issue of inventorship for the elected claims and amend inventorship appropriately if the elected restriction is made final.

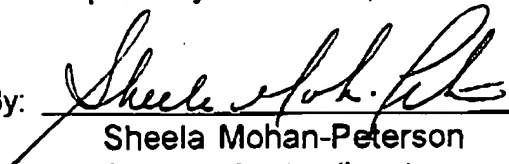
Applicants reserve the right to file subsequent applications claiming the non-elected subject matter and do not waive any of their rights or abandon any non-elected subject matter. Since Applicants have fully and completely responded to the Restriction Requirement and have made the required election, this application is now in order for early action.

If the Examiner believes that a telephonic conference would aid the prosecution of this case in any way, please call the undersigned.

Respectfully submitted,

Date: October 19, 2001

By:



Sheela Mohan-Peterson
Attorney for Applicants
Reg. No. 41,201

DNAX Research Institute
901 California Avenue
Palo Alto, California, 94304-1104
Tel. No. (650) 496-6400
Fax No.: (650) 496-1200

Encl.:

Clark, Immunol. Today 21, 397 (2000).

Fig. 10-15 in Abbas, et al. (2000) Cellular and Molecular Immunology, 4th ed.,
W.B. Saunders Co., N.Y., p 230.

Part of
#9

FOURTH EDITION

CELLULAR AND MOLECULAR IMMUNOLOGY

Abul K. Abbas, MBBS

Professor and Chair
Department of Pathology
University of California—San Francisco School of Medicine
San Francisco, California

Andrew H. Lichtman, MD, PhD

Associate Professor of Pathology
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Jordan S. Pober, MD, PhD

Professor of Pathology, Immunobiology, and Dermatology
Yale University School of Medicine
New Haven, Connecticut

W.B. SAUNDERS COMPANY

A Harcourt Health Sciences Company
Philadelphia London New York St. Louis Sydney Toronto

230 Section III MATURATION, ACTIVATION, AND REGULATION OF LYMPHOCYTES

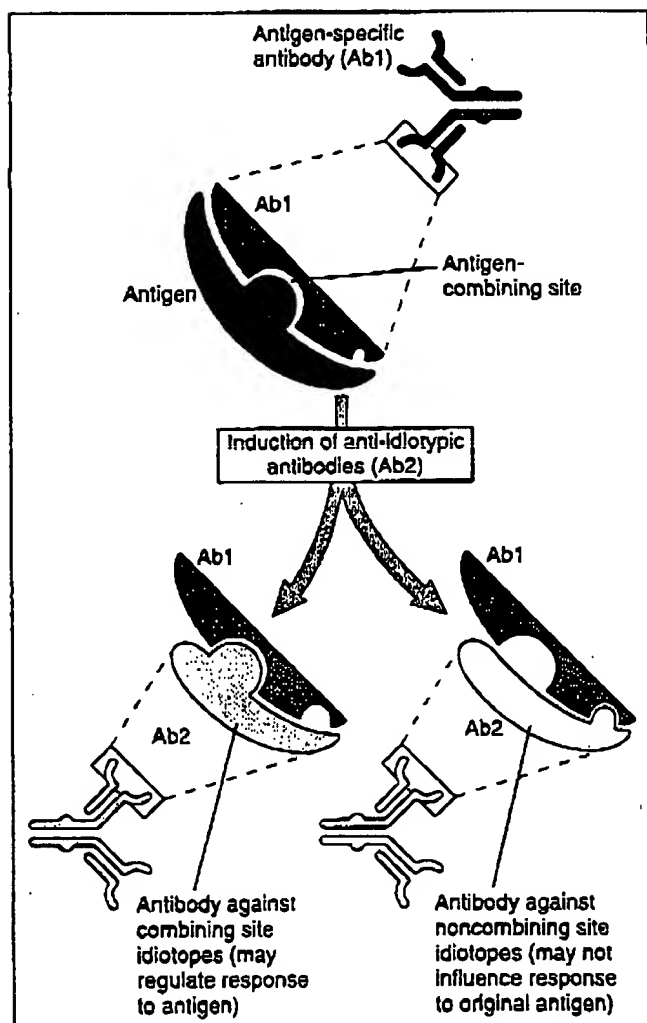


Figure 10-15 Idiotypes and anti-idiotypic antibodies.

The combining site of an antibody (Ab1) specific for an antigen has a unique shape that is complementary to the antigen. Anti-idiotypic antibodies (Ab2) may recognize the combining site of Ab1, in which case they may influence responses to the antigen, or they may recognize unique idiotypic determinants of Ab1 that are not part of the combining site.

SUMMARY

- Immunologic tolerance is unresponsiveness to an antigen induced by the exposure of specific lymphocytes to that antigen. Tolerance to self antigens is a fundamental property of the normal immune system, and the failure of self-tolerance leads to autoimmune diseases. Antigens may be administered in ways that induce tolerance rather than immunity, and this may be exploited for the prevention and treatment of transplant rejection and autoimmune and allergic diseases.
- Central tolerance is induced in the generative lymphoid organs (thymus and bone marrow) when immature lymphocytes encounter self antigens present in these organs. Peripheral tolerance occurs when mature lymphocytes recognize self

antigens in peripheral tissues under particular conditions.

- The principal mechanisms of tolerance are deletion (apoptotic cell death), anergy (functional inactivation), and suppression by regulatory T cells. Some self antigens may be ignored by the immune system, and they elicit no detectable reaction.
- In T lymphocytes, central tolerance (negative selection) occurs when double-positive thymocytes with high-affinity receptors for self antigens recognize these antigens in the thymus. Several mechanisms account for peripheral tolerance in mature T cells. In CD4⁺ T cells, anergy is induced by antigen recognition without adequate costimulation and by recognition of altered forms of the native antigen. Repeated stimulation of T cells by persistent antigens results in activation-induced cell death. Some tolerogenic antigens activate suppressor T cells, which inhibit immune responses mainly by producing immunosuppressive cytokines.
- In B lymphocytes, central tolerance is induced when immature B cells recognize multivalent self antigens in the bone marrow. The usual result is apoptotic death of the B cells or the acquisition of a new specificity, called receptor editing. Mature B cells that recognize self antigens in the periphery in the absence of T cell help may be rendered anergic or are excluded from lymphoid follicles and cannot be activated by antigen.
- Immune responses to foreign antigens decline with time after immunization. This is mainly because of apoptosis of activated lymphocytes that are deprived of survival stimuli as the antigen is eliminated and innate immunity wanes. Various active mechanisms of lymphocyte inhibition may also function to terminate immune responses.

Selected Readings

- Goodnow CC, JG Cyster, SB Hartley, SE Bell, MP Cooke, JI Healy, S Akkaraju, JC Rathmell, SL Pogue, and KP Shokat. Self-tolerance checkpoints in B lymphocyte development. *Advances in Immunology* 59:279-368, 1995.
- Healy JI, and CC Goodnow. Positive versus negative signaling by lymphocyte antigen receptors. *Annual Review of Immunology* 16:645-670, 1998.
- Klinman NR. The "clonal selection hypothesis" and current concepts of B cell tolerance. *Immunity* 5:189-195, 1996.
- Lenardo M, FKM Chan, F Hornung, H McFarland, R Siegel, J Wang, and L Zheng. Mature T lymphocyte apoptosis—immune regulation in a dynamic and unpredictable antigenic environment. *Annual Review of Immunology* 17:221-253, 1999.
- Matzinger P. Tolerance, danger, and the extended family. *Annual Review of Immunology* 12:991-1045, 1994.
- Miller JFAP, and RA Flavell. T cell tolerance and autoim-